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Courvalin et al., ASM News 1992, 58:368-375

Evers et al., 1993, Gene, 124:143-144

Quinn et al., 1989, Antimicrob. Agents Chemother. 33:1451-1456.

Rice et al., 1991, Antimicrob. Agents Chemother. 35:1243-1244

Sahm et al., 1989, ~~J. Clin, Microbiol.,~~ 33:1588-1591 Antimicrob Agents Chemother

Sahm et al., 1990, Antimicrob. Agents Chemother. 34:1846.-1848

Neu et al., 1992, Science, 257:1064-1073

Jorgensen, 1993, Diagn. Microbiol. Infect Dis 16:245-249

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Selection of Antimicrobial Agents for Routine Testing in a Clinical Microbiology Laboratory

James H. Jorgensen

Each clinical microbiology laboratory must establish its own standard battery of antimicrobial agents to be tested routinely on clinical isolates of various organism groups. Some choices are based upon the intrinsic activities of antimicrobial agents for a particular group of organisms, for example, agents primarily active against either Gram-positive or Gram-negative bacteria. For final selection of limited batteries of agents for routine testing, however, it is necessary to use additional criteria based upon physician prescribing patterns and the availability of antimicrobial agents in a particular institution. A fundamental principle in the selection process should be routine testing and reporting of those antimicrobial agents that physicians actually use, that is, the institution's formulary agents. Testing of the most appropriate drugs for an institution may be complicated by lack of availability of some antimicrobial agents among the standard panels offered by automated instrument or commercial test system manufacturers. The laboratory should develop its final test batteries in consultation with the infectious disease and pharmacy services and the pharmacy and therapeutics and infection-control committees of the medical staff. These choices should not be made based upon the most convenient selection of drugs from the laboratory's perspective or based upon pharmaceutical industry promotional efforts.

INTRODUCTION

The clinical microbiology laboratory plays a key role in antimicrobial agent selection and use by physicians. One of the most important tasks of the laboratory is the performance of routine antimicrobial susceptibility testing on significant bacterial isolates. While performing reproducible, standardized testing is essential, the laboratory has a responsibility to test and report those antimicrobials that are most appropriate for the organism isolated and for the clinical practice setting in which the laboratory functions. The battery of antimicrobial agents tested routinely by the laboratory will depend in large part on the type of patients cared for by the facility and the types of organisms most likely to be isolated from those patients. The routine testing battery employed in a large medical center that specializes in the care of immunosuppressed patients may be substantially different from the battery tested by a laboratory that supports mainly an ambulatory outpatient practice in which only community-acquired infections are seen. In the former circumstance it is likely that there will be an emphasis on testing broad-spectrum, parenteral agents including those active against *Pseudomonas aeruginosa*, whereas in the latter situation it would be more appropriate to test oral antimicrobials or parenteral agents with long pharmacokinetic half-lives.

In many institutions, the formulary is determined by a pharmacy and therapeutics committee of the medical staff. The existence of a *closed formulary* means that certain drugs have been selected by the committee for routine use in that institution, and that other agents are not readily available on a routine basis. The antimicrobial agent formulary is an important starting point for selection of the laboratory's routine susceptibility testing battery.

SELECTION OF ANTIBIOTICS FOR THERAPY

To understand the impact of antimicrobial agent susceptibility testing and reporting, it is important to

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be aware f the time sequence in which they are prescribed. The use of antimicrobial agents can be categorized as either prophylactic, empiric, c: culture (and susceptibility test) directed. Antimicr bial agents for prophylactic use are most often selected based on the type of surgery or invasive procedure to be performed (whether "dirty" or "clean") and the antimicrobial agents that provide coverage of the organisms that would be most likely to give rise to an infection following the procedure if prophylaxis were not employed. Such decisions are often made based upon the recommendations of national medical (or surgical) specialty groups or on the experience or preference of the physician performing the procedure. Antimicrobial susceptibility testing affects the choices of prophylactic antibiotics only to the extent that the laboratory documents the susceptibilities of the microorganism groups of interest on a routine basis through publication of the institution's antibiograms. These periodic reports should detail the "typical" susceptibility of the organisms actually encountered in that facility to a number of antimicrobial agents. Careful review of such data allows clinicians to determine the degree of antimicrobial agent resistance encountered in that institution in the species most relevant to their specific practice specialty. While only in a retrospective sense, susceptibility testing nevertheless affects choices of prophylactic agents in this manner.

A patient presenting with an infection serious enough to require systemic antimicrobial therapy is generally started on an agent empirically. This is based upon the clinician's judgment of the most likely infectious agent(s), the likely susceptibility of those organisms, the site and severity of the infection, and the patient's immune status. This initial empiric choice of antimicrobial agent is influenced by the microbiology laboratory only through provision of a few rapid tests such as examination of Gram-stained smears of infected body fluids or other very rapid tests, for example, latex agglutination tests for bacterial antigens in the cerebrospinal fluid, direct DNA-probe tests, and so on. The laboratory's published antibiograms are also very helpful in rational decisions regarding empiric antimicrobial therapy. From 2 to 3 days after empiric therapy has been initiated, the isolation and testing of the patient's bacterial pathogens are likely to be complete enough to allow reconsideration of the appropriateness of the empiric antimicrobial agent choice(s). At the time that specific susceptibility data become available, there is an opportunity for the physician to change to a more activ agent (if resistance has been documented by in vitro testing) or to refine the drug selection to a narrower-spectrum, less toxic, or less costly choice.

A number of factors contribute to physicians' decision making when antimicrobial agent ch ices are made at any of the temporal points described above. Perhaps the first selection factor is the physician's past experience with the use of certain antibiotics. Obviously, a physician is unlikely to prescribe a drug that has not appeared to work well previously in that physician's patients. In addition, few physicians who are not infectious diseases specialists can claim familiarity with subtle spectrum differences among all of the antimicrobial agents presently available or with the exact dosages and administration intervals of more than a few drugs. Likewise, physicians may have only a general sense of the relative cost differences among drugs. It is likely that physicians learn to use well only a small number of different antimicrobial agents (perhaps <10). Physicians may also turn to respected colleagues (perhaps infectious disease specialists) for advice regarding those drugs that would be most important in their practice specialty, or for assistance in the use of unfamiliar drugs for unusual or recalcitrant infections.

Other factors that contribute to physicians' decision making include information gained during attendance at medical meetings and symposia and from reading journal articles related to the use of antimicrobial agents. Certain of these, however, may have been supported by industry and designed to emphasize only the most positive aspects of a new agent. Also not to be underestimated are the effects of direct industry promotional efforts on physicians. Busy practitioners may be quite satisfied to be advised of the attributes of the latest antimicrobial agent from a familiar, local pharmaceutical representative. Some physicians may simply "try" the newest antimicrobial agents on certain of their patients to gain personal experience with the new drug or to see whether it might be better accepted or tolerated by certain of their patients.

The most specific and relevant information for a particular patient is made available by the laboratory when it performs an in vitro susceptibility test on a patient's unique bacterial isolate versus several different available antimicrobial agents. Although the susceptibility report is often not available when initial prescribing decisions must be made, the susceptibility information should be reviewed on the second or third day of therapy to support an empiric decision, or to allow selection of a more active or narrower-spectrum agent. Therefore, the selection of agents for inclusion in the microbiology laboratory's routine patient reports can have a significant affect on the final selection of antimicrobial agents used for therapy. Some have claimed that physicians pay little attenti n to antimicrobial susceptibility re- p rts (Edwards et al., 1973), although at least two

studies have documented that antimicrobial therapy for bacteremia was altered to some degree by physicians in response to susceptibility reports from the laboratory (Doern et al., 1982; Weinstein et al., 1983).

If the most appropriate drugs are not tested, patients may be denied access to optimal therapy, while, at the same time, if agents are tested that are not routinely available due to formulary restrictions, the laboratory's efforts have been wasted. It should go without saying that pressure from pharmaceutical representatives to test nonformulary drugs for promotional purposes should be resisted.

SELECTING ROUTINE TESTING BATTERIES

When determining the specifics of a laboratory's routine susceptibility testing battery, several principles that should be in the forefront of the decision making include the fact that the laboratory has a responsibility to test those agents included on the institutional formulary and those that physicians actually use on a day-to-day basis. Generally these are one in the the same, but it should be verified that the approved formulary actually represents current prescribing practices. There may be instances in which the formulary has not kept pace with physicians' usage through writing of nonformulary prescriptions. Costs of antibiotics may also change periodically, causing additions or deletions to the formulary. Antibiotic costs may vary substantially among institutions due to bidding practices or other special group purchasing agreements. Thus, national cost information (*Med Lett*, 1992) may be used as a general guide, but the institution's actual costs may be significantly different. When comparing costs, it is also important that equivalent dosages, dosing frequencies, and administration costs be compared.

The organism to be tested dictates to a some degree the appropriate antimicrobial agents for testing. The National Committee for Clinical Laboratory Standards (NCCLS, 1990a–c) lists the antimicrobial agents appropriate for testing of Enterobacteriaceae, *Pseudomonas*, and other glucose nonfermenters, staphylococci, enterococci, streptococci, *Haemophilus* spp., *Neisseria gonorrhoeae*, and anaerobic bacteria. The NCCLS has recently extended this listing to include recommendations regarding which agents are the most important to test routinely and those that may be tested only by special request or circumstance. Likewise, the critiques that follow the College of American Pathologists (CAP) proficiency surveys often emphasize the most important antimicrobial agents for routine testing with various organisms. Other potential sources for guidance on this subject include the *Medical Letter*, recent review articles published in well-respected, peer-reviewed journals, and possibly position statements from medical specialty groups.

It is important for the laboratory to have the support of the medical staff and pharmacy in the final selection of antimicrobial agents for routine testing and reporting. It may be expedient for the laboratory to establish a "draft" listing of those agents that seem to be the most appropriate for each organism group based upon the information sources mentioned above. The provisional test batteries could then be submitted to the institution's pharmacy and therapeutics committee and to the directors of the infectious disease and pharmacy services for comment and consensus approval. This approach may be more rewarding than merely asking of those groups, "Which drugs do you think the laboratory should test on a routine basis?"

Another important step in selecting the routine testing batteries is to determine the availability of antimicrobial agents for testing by the laboratory's routine methodology. If the routine testing method is the Bauer–Kirby disk diffusion procedure, there should not be a problem in obtaining the appropriate disks for testing virtually any grouping of agents. From a practical point of view, however, not more than 12 drugs can be tested on a 150-mm Mueller–Hinton agar plate. Thus, if a routine testing battery contains more than 12 agents, a second plate would be required, thus doubling the cost of each patient's susceptibility test. In an analogous manner, if the laboratory prepares its own broth microdilution panels, the limiting factor is the availability of only 96 wells in standard plastic trays. While perhaps less of a problem than with disk diffusion plates, it may be difficult to include more than 12 agents in a microdilution tray if full concentration ranges of each agent are to be tested. Therefore, with either method, there are practical limits to how many antimicrobial agents may be included in the routine test batteries and still achieve maximum diagnostic and economic benefit from the test.

A review of participant responses in recent CAP proficiency surveys indicates that 50% or more of US laboratories now use a commercial microdilution or automated system for their routine susceptibility testing. The laboratory must determine whether a desired battery of antimicrobial agents is available among the standard panels offered by a particular device manufacturer. This represents a problem, since the in vitro diagnostics device industry has also struggled with decisions regarding which groups of drugs t make available in individual systems. Manufacturers have dealt with this problem in several ways: either by offering a number f different stan-

TABLE 1 Potential Routine Test Battery for *Staphylococcus* spp.

Penicillin	Ciprofloxacin or ofloxacin
Oxacillin	Clindamycin
Cefazolin	Trimethoprim–sulfamethoxazole
Vancomycin	
Erythromycin	

dard drug-panel configurations in trays or cards, by including fewer dilutions of each drug in a panel (thus allowing more drugs to be tested per tray or card), or by making available a set of two panels to be used together to allow testing of an extended number of drugs at a price that reflects a deep discount for the second half of the panel.

Despite these options, the ever-increasing number of new agents makes it unlikely that every laboratory can find its exact choice of antimicrobial agents among a manufacturer's standard offerings. However, the availability (or lack thereof) of certain drugs in commercial test batteries should not be the basis for final decisions regarding an institution's standard testing battery. Alternative solutions to this problem include having a manufacturer prepare "custom" panels that match precisely the institution's formulary, or perhaps testing of other antimicrobial agents that have activities very similar to the desired formulary drugs. Tables 1 of both the NCCLS disk diffusion and aerobic dilution testing documents (NCCLS, 1990b and c) include groups of antimicrobial agents with nearly identical activities that might offer alternatives for testing in commercial test systems. The use of custom panels is theoretically desirable although more expensive than purchase of "standard" test panels. The latter solution is more economical, but limited somewhat by the possiblity of some very slight differences in activity between the desired drug and the agent tested to represent it. These decisions must be addressed by each laboratory in its own way and likely will represent a continuing problem as more new drugs become available and institutional formularies react accordingly.

TABLE 2 Potential Routine Test Battery for *Enterococcus* spp. and *Streptococcus* spp.

Enterococcus	*Streptococcus*
Ampicillin or penicillin	Penicillin
Vancomycin	Cefazolin or cephalothin
Ofloxacin or ciprofloxacin[a]	Vancomycin
HLGR and HLSR[b]	Ofloxacin
	Clindamycin
	Erythromycin

[a]Urinary isolates only.
[b]High-level gentamicin and streptomycin resistance on blood culture isolates only.

TABLE 3 Potential Routine Test Battery for Aerobic Gram-Negative Bacilli

Ampicillin
Ticarcillin–clavulanic acid or ampicillin–sulbactam
Mezlocillin or piperacillin[a]
Cefazolin
Cephalothin[a]
Cefotetan, cefmetazole, or cefoxitin
Cefotaxime, ceftriaxone, or ceftizoxime
Ceftazidime[b]
Gentamicin or amikacin
Ciprofloxacin or ofloxacin
Trimethoprim–sulfamethoxazole

[a]To represent the oral cephalosporins cefaclor, cephalexin, cephadroxil, and cephradine.
[b]*Pseudomonas* spp. only.

The above discussion is intended to represent general guidance and background information regarding the selection of antimicrobial agent batteries for routine testing. This author cannot presume to know which antimicrobial agents are the most important and relevant for all institutions. It may be useful, however, for the purpose of this presentation to describe example test batteries with several alternative choices for the major organism groups. Tables 1–5 indicate the author's personal opinions regarding antimicrobial agents that might be selected as routine testing batteries for five groups of organisms. The selections are based on the author's opinions regarding the clinical and cost effectiveness of available agents for these major organism groups. In several instances, choices are indicated that would be made based upon which of the similar agents were included in the formulary. In all cases, the potential test batteries do not include more than 12 drugs. Certain conspicuous omissions from these batteries may be considered as necessary agents for

TABLE 4 Potential Routine Test Battery for Outpatient Therapy of Aerobic Gram-Negative Bacilli

Ampicillin
Amoxicillin–clavulanic acid
Cephalothin[a]
Cefuroxime or cefixime
Ceftriaxone
Gentamicin
Ciprofloxacin or floxacin
Trimeth prim–sulfameth xazole

[a]To represent the oral cephalosporins cefaclor, cephalexin, cephadroxil, and cephradine.

TABLE 5 Potential Routine Test Battery for *Haemophilus influenzae*

Ampicillin
Amoxicillin–clavulanic* acid or ampicillin–sulbactam
Cefixime,* cefuroxime,* or cefaclor*
Cefotaxime or ceftriaxone
Ciprofloxacin* or ofloxacin*
Chloramphenicol
Trimethoprim–sulfamethoxazole*

*Oral agents only for therapy of localized infections.

routine testing by some readers. Likewise, it would be necessary to have a supplemental battery of several additional agents for secondary testing of those Gram-negative bacteria found to be resistant to the basic drug battery.

Finally, it is important to recognize that some special needs must be accommodated. Certain areas of a hospital may harbor especially resistant organisms that require the testing of more potent antimicrobial agents, and certain patient (for example, pediatric, obstetric, or oncology) or physician groups (for example, ophthalmology) may require antimicrobial agents that differ from those of the majority of the laboratory's users. These "special batteries" must be devised through close communication with the physicians responsible for those areas. This may mean that special batteries of antimicrobial agents are tested routinely or by specific request in those situations. The laboratory must maintain some degree of flexibility in order to serve its many users.

In summary, the final choices regarding routine antibiotic test batteries must be made by cooperative efforts of the microbiology laboratory, the infectious disease and pharmacy services, and the pharmacy and therapeutics and infection-control committees (NCCLS, 1990b and c). All individuals must recognize the necessity of periodic changes to the formulary as clinical needs change and new drugs are introduced. This also means that the microbiology laboratory's standard susceptibility testing batteries are likely to require frequent revisions.

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